NOVARTIS

4395 '02 MAY -6 A10:15

May 3, 2002

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20857

Re: Docket 01P-0574/CP1

To whom it may concern:

Novartis Pharmaceuticals Corporation ("Novartis"), provides this response to the comments of Ben Venue Laboratories, Inc. ("Ben Venue") which were dated April 3, 2002 and submitted to the citizen petition assigned to the docket referenced above.[1] In Ben Venue's petition, they specifically seek a determination that "discontinued labeling for Octreotide Acetate Injection was not withdrawn for safety or effectiveness reasons" and, additionally, that use of that labeling by a generic product would not render that product less safe or effective than Sandostatin® Injection. In its February 14, 2002 reply to that petition, Novartis provided a number of documents that show both the motive and the efforts expended in developing a safer formulation of Sandostatin Injection. Among these was the study report of a bioequivalence trial comparing the original formulation to the safer preparation. In one pertinent part, this report states:

> "During the clinical study of the drug it was found that (Sandostatin Injection) causes local pain at the injection site because of acetic acid which is added as an excipient. In order to eliminate the local pain, a new preparation (hereinafter called "test preparation") was developed, using lactic acid in place of acetic acid."[2]

Also provided was an excerpt from the Pharmaceutical Expert Report generated by (then) Sandoz during the development of the new formulation. Another section of that same report states:

01P-0574 RC 2

[1] Those comments were made in answer to Novartis' reply to Ben Venue's citizen petition of December 14, 2001.

[2] "Bioequivalence Study of the Two Preparations of SMS 201-995", Sandoz Pharmaceuticals, Ltd., Tokyo, Japan, March 1988.

"(I)t has been reported that (the acetic acid-containing) formulation causes pain at the injection site. The proposed new formulation was developed in order to eliminate this problem."[3]

It is clear from these citations that Novartis has consistently and directly stated its reason for developing a safer, less painful formulation of the Sandostatin® (octreotide acetate) Injection product: to respond to patient reports of pain at the site of injection. In this reply to Ben Venue's most recent commentary, Novartis hereby seeks to clarify any misunderstanding of the issues surrounding the development, submission, and approval of the currently marketed Sandostatin formulation.

The Regulations Do Not Permit the Formulation Changes Ben Venue Seeks to Re-introduce in Their Generic Octreotide Acetate Product

Ben Venue's original petition explained in detail their belief that "the key issue of (their) request related (to) the use of sodium chloride as a tonicity agent", a position they reiterated in their April 3rd letter. Additionally, in both documents, Ben Venue maintained that the re-introduction of a buffer system, which was eliminated from the currently-approved formulation and deleted from the labeling of the reference listed drug ("RLD"), is permitted in a generic product by the regulations and "would be properly evaluated during the ANDA review process." [4] An examination of what constitutes "proper evaluation" under the regulations follows below.

It is important to note that, in pertinent part, the regulation Ben Venue cited to support its proposed changes in inactive ingredients states:

> "*Inactive ingredient changes permitted in drug products intended for parenteral use.* Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that *the differences do not affect the safety of the proposed drug product.*" 21 CFR 314.94(a)(9)(iii). (emphasis at end added)

This is not the only place in the CFR that confirms FDA's commitment to the maintenance of the same degree of safety in an ANDA-based product that was shown by its RLD. Under 21 CFR 314.127(8)(ii)(B) it is noted that:

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[3] "Sandostatin® Ampoules 0.1mg/1ml (Lactic Acid/Mannitol Formulation), Part 1 C: Expert Report on 1. Chemical and Pharmaceutical Documentation", Sandoz Ltd., Basle, Switzerland, 36/40Dr. DS, June 14, 1989, at Format 2a. A substantially identical volume was prepared in connection with the 0.5mg/mL product.

[4] In their most recent filing, they also assert that the outdated Sandostatin formulation "was not withdrawn for safety or efficacy," which is a decision that is beyond their authority to make.

> "FDA will consider an inactive ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and will refuse to approve the abbreviated new drug application unless it contains the same inactive ingredients, other than preservatives, buffers, and antioxidants, in the same concentration as the listed drug, and, *if it differs from the listed drug in a preservative, buffer, or antioxidant, the application contains sufficient information to demonstrate that the difference does not affect the safety of the drug product.*" (emphasis added)

FDA then goes on to explain what it considers to be the aforementioned "sufficient information" by refusing to waive the requirement for the submission of evidence of in vivo bioavailability or bioequivalence unless the ANDA-based product "(c)ontains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application." 21 CFR 320.22(b)(1)(ii). Indeed, at the time the statutory amendments codified in the CFR were promulgated, FDA specifically retained this restrictive language, stating that "FDA cannot always predict the consequences of minor changes." 57 Fed. Reg. 17950, [comment response no. 100] (1992).

In summary, then, the CFR requires that, at the very least, an ANDA-based parenteral product must reproduce exactly both the active and inactive ingredients of the RLD or submit in vivo bioavailability or bioequivalence data to demonstrate that any changes from the RLD formula do not affect the safety of the drug product, even if those changes occur among inactive ingredients or the constituents of buffer systems. Because of this, Ben Venue's focus on the change in isotonizing agent (from mannitol to sodium chloride) is misplaced, and its exclusion of consideration of the effect of reversion in buffer system, unjustified.

It could reasonably be maintained that a substitution of sodium chloride for mannitol to provide isotonicity might not affect the safety of the final product. Indeed, Novartis' Pharmaceutical Expert Report shows that the company itself considered using sodium chloride in its currently approved formulation.[5] Appendix 2 of Novartis' February 14th reply provides supporting excerpts from the Pharmaceutical Expert Report for the ampule product. That same appendix highlights the reason the reformulation was undertaken -- to reduce pain at the site of injection -- and documents the steps employed to generate a new formula appropriate for clinical testing.[6] With that formula finalized, Novartis then demonstrated clinically that the updated product did, in fact, reduce pain at the injection site (that study report appeared as Appendix 1of the

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[5] The original, acetic acid-buffered formulation, replaced by the currently approved product, used sodium chloride as its isotonizing agent.

[6] Additional excerpts of that report are appended to this letter (see Appendix 1). Appendix 3 of Novartis' 2/14/02 letter also provides publications of studies wherein the placebo utilized the old acetic acid/sodium hydroxide buffer. These studies consistently recorded pain at the injection site across study groups, with the incidence of placebo complaints not far removed from those of patients receiving the active drug. This is not the case for testing of the revised, currently marketed formulation.

February 14th letter). FDA already has the full Expert Report on file, as well as the report of the clinical study providing evidence of reduction of pain, and the Reviewing Division has the best perspective from which to assess these data. Novartis believes that the demonstrated reduction in injection site pain equates to an increase in safety for these patients who must self-administer the drug multiple times daily.[7]

Because regulatory requirements, formulation issues, and clinical data all point to retention of the currently-approved buffer system as the safer alternative in the Sandostatin Injection formulation, neither the clinical nor the regulatory acceptability of the outdated buffer system in an ANDA-based octreotide acetate injection product can be assumed. Moreover, according to the CFR and based on available data, a technical review as the sole evaluation of the proposed return to the outdated formulation would ignore the available clinical data and, as noted above, violate the regulations. Therefore, only the product that includes the lactic acid/sodium bicarbonate buffer system should be permitted.

Novartis/Sandoz Worked With FDA to Bring the Improved Formulation to Its Patients

Octreotide acetate was, and currently remains, the most important treatment option for patients diagnosed with the indications carried in its labeling. When only the initially approved formulation was available, that product's safety profile was acceptable. Once an improved form was identified, Novartis/Sandoz co-operated with FDA to bring that product to the public with all appropriate speed.

In its April 3rd letter, Ben Venue repeatedly stresses its lack of awareness of the process by which the improved formulation replaced the now deficient one in the marketplace. During the time of that transition, Novartis relied on FDA to dictate the appropriate and responsible steps by which this was accomplished, and responded quickly to any issues that were identified. The fact remains that regression now to a formulation that has been shown to be more painful should not be permitted.

FDA Is In The Process Of Reconsidering Its Guidance for Industry Concerning the Referencing of Discontinued RLD Labeling in ANDAs

It was recently reported[8] that FDA's Chief Counsel has stopped work on, and raised objections to, the draft "Guidance for Industry Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications." The cessation of development of this Guidance document was reported to be related to the Chief Counsel's question regarding whether FDA has actually been granted statutory authority to permit generic products to reference the discontinued labeling of innovator products in an ANDA. These questions and concerns may be expected to have ramifications for the approval of ANDAs for generic duplicates of Novartis' Sandostatin Injection product and Novartis

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[7] Indeed, patients who hesitate or neglect to inject themselves according to their prescribed regimen because of the discomfort involved will also experience a decrease in efficacy,

[8] The Pink Sheet, April 8, 2002, page 24.

awaits the publication of further information regarding FDA's determinations. While this new issue is unfolding, however, it appears advisable to suspend any labeling determinations that could fall within the purview of that document.

Novartis hopes that the above information further clarifies the issues surrounding the development and approval of the current Sandostatin ® (octreotide acetate) Injection product. Please feel free to contact the undersigned, on (973) 781-8697, if there are any questions or if additional information is required.

Respectfully submitted,

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Associate Director
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cc: Gary Buehler -- HFD 600
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SANDOZ

SANDOSTATIN® AMPOULES 0.1 MG/1 ML

(LACTIC ACID/MANNITOL FORMULATION)

PART I C: EXPERT REPORT ON

1. CHEMICAL AND PHARMACEUTICAL DOCUMENTATION

SANDOZ LTD, BASLE, SWITZERLAND
3640/Dr.DS
June 14, 1989

I. CRITICAL EVALUATION OF THE METHODOLOGY, RESULTS AND CONCLUSIONS

1. Introduction

2. Composition of the product

SANDOSTATIN® Ampoules 0.1 mg/ml is a pharmaceutical form of the active ingredient OCTREOTIDE, a synthetic octapeptide analogue of the natural somatostatin.

An ampoule formulation of this active ingredient in the same strength is already marketed in several countries. In is an aqueous solution with an acetate buffer system. The present formulation was developed in order to replace the initially developed formulation since it was reported from clinical studies that the acetate buffer formulation causes pain at the injection site.

Format 2a

The new formulation is also an aqueous solution which contains lactic acid/sodium hydrogen carbonate as pH regulating system and mannitol as isotonising agent. The pH of the solution is 4.2, the same pH as for the acetate formulation.

Format 1

The choice of the new formulation is based on a pH profile test in which several formulations were compared. These formulations comprised classical ingredients for parenteral solution. From this study it could be confirmed that pH 4.2 is the best pH regarding stability of SANDOSTATIN® Ampoules.

Format 2a

The two isotonising agents tested, mannitol and sodium chloride, had no influence on the stability. Sandoz Ltd decided to select mannitol. The gas protection has been selected to prevent potential oxydation of the active ingredient.

Format 2b

The lactic acid/mannitol formulation was found to produce less pain at the injection site. This can be explained as follows:

I. CRITICAL EVALUATION OF THE METHODOLOGY, RESULTS AND CONCLUSIONS

2. Composition of the product (Cont.)

the physiological pH of about 7.2 at the injection site is more rapidly reestablished after injection of lactic acid than after injection of acetic acid. Lactic acid (pK 3.86) has a lower buffer capacity than acetic acid (pK 4.76) at pH 4.2 (lactic acid is partly neutralised with sodium hydrogen carbonate to pH 4.2, acetic acid is buffered to pH 4.2 by sodium acetate).

The implementation of these changes in the composition does not affect the quality of SANDOSTATIN® Ampoules.

Format 2b

Format 3

Format 3

Format 1